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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/523,723	TANAKA ET AL.	
	Examiner	Art Unit	
	Katherine Salmon	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *4,10,11 and 13-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-9 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/06; 11/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of Group 1, Claims 1-3, 5-9 and 12 and the specific SNP at position 80 of exon 3 in SEQ ID NO. 3 in the reply filed on 10/09/2007 is acknowledged.

The traversal is on the ground(s) that all the sequences were examined during the International stage of the PCT and therefore should be examined together in the US application (p. 17 1st full paragraph). The reply further asserts that the Seq ID numbers share a relationship of linkage disequilibrium with each other (p. 17 2nd paragraph). These arguments have been thoroughly reviewed but have not been found persuasive. The PCT application was not prepared by the USPTO, however, in the instant case, the reasons for separating the SEQ ID Numbers into specific groups has been discussed in the requirement for restriction (mail date 8/08/2007).

Specifically each combination of SEQ ID Numbers is a separate group because each combination of SEQ ID Numbers fail to share a specific technical feature (p. 3-4 of requirement for restriction). As discussed in the requirement for restriction, each combination of SNP positions are drawn to a different gene and are not homologous to each other. Therefore a search of one combination of SNPs would not provide information on another combination of SNPs. The mere fact that there is linkage disequilibrium is not sufficient to show a shared technical relationship because the sequences do not share a common property (e.g. the sequences all detect different genes or different regions of a gene) and do not share a common structure (e.g. the sequence for each mutation is different).

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-32 are pending. Claims 4, 10-11 and 13-32 have been withdrawn as being drawn to a nonelected invention. Specifically Claim 4 has been withdrawn as being drawn to a SNP combination not elected in the reply filed on 10/09/2007.

3. An action on the merits for Claims 1-3, 5-9, and 12 is set forth below.

Specification/New matter

4. The amendment filed 10/09/2007 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The amendment to the specification is to amend "a C/A polymorphism at nucleotide 81 in the nucleotide sequence of exon 3 of the LT-α gene shown in SEQ ID No. 3" to "a C/A polymorphism at nucleotide 80 in the nucleotide sequence of exon 3 of the LT-α gene shown in SEQ ID No. 3".

The original disclosure (11/29/2005) did not contain to "a C/A polymorphism at nucleotide 80 in the nucleotide sequence of exon 3 of the LT-α gene shown in SEQ ID No. 3".

The response to amendment asserts that the change is a typographical error (p.

16 1st paragraph). However on p. 13 1st paragraph, the specification asserts that the C/A polymorphism at nucleotide 81 of the nucleotide sequence of exon 3 of the LT-A gene showing in SEQ ID No. 3 causes an amino acid mutation from threonine to asparagine.

. Threonine is ACT, ACC, ACA, or ACG. Asparagine is AAT or AAC. Accordingly there is no way to mutate the 80th nucleotide and get asparagine.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-3, 5-9, and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3 and 5-9 are indefinite because the claims do not recite a clear nexus between the preamble of the claims and the process steps of the claims. The preamble states a method for determining an inflammatory disease. The last method step is detecting at least one gene polymorphism. Therefore the last step does not provide method steps for determining an inflammatory disease, rather it provides a step for detecting a polymorphism.

Claims 3, 5, 7- 9, and 12 are unclear over the phrase "80 in the nucleotide sequence of exon 3 of the LT-α gene shown in SEQ ID No. 3". It is unclear if nucleotide

position is in the nucleotide sequence of exon 3 or the nucleotide position of SEQ ID No. 3.

Claim 5 is unclear. Claim 5 is drawn to a substitution of at least one of the nucleotides 80 to 82 wherein the amino acid sequence is mutated from threonine to asparagine. The nucleotide sequence of nucleotide 80-82 is ACC which is threonine. The nucleotide sequence of asparagine is AAT or AAC. Therefore the only nucleotide sequence which can change is nucleotides 81 and 82. If nucleotide 81 changes to an A then the sequence codes for asparagine. If nucleotide 81 changes to an A and nucleotide 82 changes to a T then it also codes for asparagine. Asparagine requires that the first nucleotide be an A and therefore nucleotide 80 cannot be mutated.

Claim 12 is unclear over the preamble of "analyzing the expression state of LT-A". The method step of Claim 12 is detecting "a C/A polymorphism at nucleotide 80 in the nucleotide sequence of exon 3 of the LT-α gene shown in SEQ ID No. 3". It is unclear how the detection step analyzes the expression state.

Claim Rejections - 35 USC § 112/New Matter

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3, 7-9, 12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Upon review of the specification and based on the objection to the specification for new matter as discussed above, the specification does not appear to provide support for the recitation of "a C/A polymorphism at nucleotide 80 in the nucleotide sequence of exon 3 of the LT-α gene shown in SEQ ID No. 3".

7. Therefore there is no support in the specification for the amendments to the claims incorporating "a C/A polymorphism at nucleotide 80 in the nucleotide sequence of exon 3 of the LT-α gene shown in SEQ ID No. 3".

The amendment to the specification is to amend "a C/A polymorphism at nucleotide 81 in the nucleotide sequence of exon 3 of the LT-α gene shown in SEQ ID No. 3" to "a C/A polymorphism at nucleotide 80 in the nucleotide sequence of exon 3 of the LT-α gene shown in SEQ ID No. 3".

The original disclosure (11/29/2005) did not contain to "a C/A polymorphism at nucleotide 80 in the nucleotide sequence of exon 3 of the LT-α gene shown in SEQ ID No. 3".

The response to amendment asserts that the change is a typographical error (p. 16 1st paragraph). However on p. 13 1st paragraph, the specification asserts that the C/A polymorphism at nucleotide 81 of the nucleotide sequence of exon 3 of the LT-A gene showing in SEQ ID No. 3 causes an amino acid mutation from threonine to asparagine.

. Threonine is ACT, ACC, ACA, or ACG. Asparagine is AAT or AAC. Accordingly there is no way to mutate the 80th nucleotide and get asparagine.

These amendments to the claims, therefore, constitute new matter.

8. Claims 1-3, 5-9, and 12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-2, 5-6 are broadly drawn to determining an inflammatory disease comprising detecting any mutation LT-α gene. Claims 1-3, 5-9, and 12 are broadly drawn to determining an inflammatory disease in any organism.

The specification discloses a method for determining inflammatory diseases involving identifying gene polymorphism associated with the disease (p. 3 2nd paragraph). The specification discloses that the invention has typed SNPs within a population of about 1000 myocardial infarction patients and a control group of about 1000 persons by multiplex PCR-invader assay (p. 3 3rd paragraph).

Therefore the claims encompass an extremely large genus of possible polymorphism and mutations. The claims encompass deletions, insertions, substitutions, and SNPs. The specification detects that of the 26 SNPs detected on 1133 myocardial infarction patients only 3 SNPs in LT-A had a statistically significant

association (p. 23-25). Therefore the claims encompass an extremely large genus of possible mutations. The specification does not teach an association of the 26 SNPs described and detection of inflammatory diseases.

The term "inflammatory disease" includes a broad genus of possible disease. The specification asserts that inflammatory disease is not specifically limited, as long as it is a disease confirmed to induce cell adhesion factors or cytokines that are know to correlate with pathologic conditions of inflammation (p. 13 last paragraph).

The specification provides examples of inflammatory disease include chronic articular inflammation, rheumatism, lupus, inflammatory enteritis, allergic reactions, bacterial shock, and myocardial infarction (p. 13 last paragraph).

The specification provides no predictable association between the SNPs listed in the specification and the broad scope of disease encompassed by the claims.

Accordingly, the teachings in the specification show that the lists of SNPs are not predictably association with any inflammatory disease. Additionally, the specification lacks guidance as to a statistical association with the inflammatory disease any all other possible mutations.

The claims recite the function language "determining inflammatory disease', however, the specification does not actually demonstrate the encompassed mutations determine any inflammatory disease.

Claims 1-3, 5-9, and 12 are broadly drawn to determining an inflammatory disease in any organism. The claims therefore are drawn to determining inflammatory diseases in any organism. This is a large genus which encompasses humans, mice,

dogs, hamsters, ect. The specification has only described 26 SNPs in a human population. Therefore the specification does not provide guidance as to what structure of the LT-A gene is shared by all organisms. Therefore there is no guidance in the specification as to which mutations are associated in all organisms.

The current claims encompass a large genus of nucleic acids which comprise mutations in the LT-A gene. The genus includes an enormous number of mutations for which no written description is provided in the specification. This large genus is represented in the specification by only the particularly named mutations of the 26 SNPS for which only three have a statistical association with a type of inflammatory disease. This data, however, does not provide for a predictable association with any inflammatory disease as is broadly claimed.

Thus, applicant has express possession of only particular mutations in LT-A gene in a genus which comprises hundreds of millions of different possibilities. Further, the applicant has express possession of any mutation in any LT-A gene in any organism. This would further expand the number of possible mutations in the genus.

No common element or attributes of the sequences are disclosed which would permit selection of sequences as polymorphisms or mutations. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a mutation with any inflammatory disease is provided.

Further, these claims expressly encompass variants including insertions, deletions, substitutions and SNPs at thousands of different sites. However, no

predictable correlation between the structural alterations of the polymorphisms or mutations disclosed and any inflammatory disease is provided by the specification.

The lack of any indication by the specification as to the function of the observed mutations and how it provides for an association with increased risk of developing any inflammatory disease leaves one of skill in the art with no predictable correlation that any mutation in the gene would have the same affect.

For example, in the post-filing art, SNPs identified in the LT-A gene have been shown not to be associated with inflammatory disease. Tobin et al. (European Heart Journal 2004 Vol 25 p. 459) teaches a method of detecting SNP from LT-A and the association with myocardial infarction (abstract). Tobin et al. tested 1052 subjects (abstract). Tobin et al. does not teach a statistically significant p-value for SNP thr26asn (p= 0.446) (Table 2 p. 462 last gene and polymorphism).

The specification has provided no teaching or guidance that would provide the skilled artisan with any indication as to which of this enormous genus of mutations are disease associated and which are not.

The specification provides no correlation between structure of the mutations and the function of such mutations with determining any inflammatory disease. The SNPs described in the specification are not representative of the genus of mutations because it is not clear which mutations would have the effect of determining any inflammatory disease.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding

genus/species situations that "Satisfactory disclosure of a ``representative number'' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: 'Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.) In the instant case, the specification fails to teach the necessary common attributes or features of the genus of encompassed mutations in view of the species disclosed. The specification fails to teach the necessary common structure of the LT-A gene of the genus of any organism in view of the species (e.g. human) disclosed. As such, one of skill in the art would not recognize that applicant was in possession of the genus of any mutation in any LT-A gene of any organism as encompassed by the broadly claimed invention.

Claim Rejections - 35 USC § 112/Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-3, 5-9, and 12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use

the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Breadth of the claims

Claim 1 is drawn to determining an inflammatory disease comprising detecting at least one gene polymorphism in lymphotoxin- α (LT-α gene). Claim 2 is drawn to a method for determining an inflammatory disease which comprises detecting at least one SNP in LT-α gene. Claim 3 is drawn to a method for determining an inflammatory disease comprising detecting SNP C/A polymorphism at nucleotide 80 in the nucleotide sequence of exon 3 of the LT-α gene shown in SEQ ID no. 3 (referred to as C723A or T26N or Thr26Ala). Claim 5 is drawn to a method for determining an inflammatory disease which comprises detecting a gene polymorphism whereby there is an amino acid change from threonine to asparagine. Claim 6 defines the disease as myocardial infaction. Claim 7 is defines the SNP position in Claim 1. Claims 8 and 9 define the method of detection and SNP position in Claim 1. Claim 12 is drawn to a method for analyzing the expression state of LT-α gene by detection of SNP C723A.

The claims are broadly drawn to determining any inflammatory disease by detection of any polymorphism of the LT-α gene. Claims 3, 7-9, and 12 are drawn to a SNP position which is not supported by the specification. The claims are drawn to detection of any mutation in any LT-α gene in any organism.

When the claims are read in light of the specification, the specification does not provide predictable guidance for any inflammatory disease by detection of any polymorphism of the LT-α gene.

The art, as presented below, that such correlations are unpredictable and population specific.

Nature of the Invention

The claims are broadly drawn to determining any inflammatory disease by detection of any polymorphism of the LT-α gene. Claims 3, 7-9, and 12 are drawn to a SNP position which is not supported by the specification.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Teachings in the Specification and state of the art

Claims 3, 7-9, and 12 are drawn to detection of "a C/A polymorphism at nucleotide 80 in the nucleotide sequence of exon 3 of the LT-α gene shown in SEQ ID No. 3". This mutational change is not supported by the specification, as discussed above, and therefore it would be unpredictable that this SNP is correlated to any

inflammatory disease.

10. The amendment to the specification is to amend "a C/A polymorphism at nucleotide 81 in the nucleotide sequence of exon 3 of the LT-α gene shown in SEQ ID No. 3" to "a C/A polymorphism at nucleotide 80 in the nucleotide sequence of exon 3 of the LT-α gene shown in SEQ ID No. 3".

The original disclosure (11/29/2005) did not contain to "a C/A polymorphism at nucleotide 80 in the nucleotide sequence of exon 3 of the LT-α gene shown in SEQ ID No. 3".

The response to amendment asserts that the change is a typographical error (p. 16 1st paragraph). However on p. 13 1st paragraph, the specification asserts that the C/A polymorphism at nucleotide 81 of the nucleotide sequence of exon 3 of the LT-A gene showing in SEQ ID No. 3 causes an amino acid mutation from threonine to asparagine.

. Threonine is ACT, ACC, ACA, or ACG. Asparagine is AAT or AAC. Accordingly there is no way to mutate the 80th nucleotide and get asparagine.

Therefore, the specification does not provide any guidance to detecting a SNP at position 80 or any correlation of this SNP to any type of inflammatory disease.

The specification discloses that LT-α gene is one of the cytokines produces during the earliest phase of the process of angiitis and it activates the cytokine cascade by inducing other mediators (p. 2 2nd paragraph). The specification discloses that these mediators are known to be involved in atheroma formation and aterma lesions (p. 2 2nd paragraph).

The specification discloses a method for determining inflammatory diseases involving identifying gene polymorphism associated with the disease (p. 3 2nd paragraph). The specification discloses that the invention has typed SNPs within a population of about 1000 myocardial infarction patients and a control group of about 1000 persons by multiplex PCR-invader assay (p. 3 3rd paragraph). However, the specification has not provided a predictable correlation of any of the typed SNPs with any inflammatory disease.

The specification discloses that the C/A polymorphism at nucleotide 81 of the nucleotides sequence of exon 3 of the LT-α gene shown in SEQ ID No. 3 causes an amino acid mutation from threonine to asparagine in codon 26 (p. 13 1st full paragraph). However, this mutational change has not been correlated with any inflammatory disease. The specification asserts a correlation between the SNP and myocardial infarction. However, the art, as presented below teaches that correlation between a specific type of inflammatory disease and a SNP cannot be extrapolated to any inflammatory disease (see Witte et al.). Post-filing art further teaches that a correlation of the amino acid change represented by this SNP is not correlated to myocardial infarction (Tobin et al.). Therefore though, the specification provides some statistical correlation between a particular SNP and a specific inflammatory disease, the post-filing correlation that this correlation is unpredictable.

The specification asserts that inflammatory disease is not specifically limited, as long as it is a disease confirmed to induce cell adhesion factors or cytokines that are know to correlate with pathologic conditions of inflammation (p. 13 last paragraph).

The specification provides examples of inflammatory disease include chronic articular inflammation, rheumatism, lupus, inflammatory enteritis, allergic reactions, bacterial shock, and myocardial infarction (p. 13 last paragraph).

Therefore the term "inflammatory disease" encompasses a myriad of diseases, each with different genetic associations. It would be unpredictable for one of skill in the art to extrapolate a correlation between a specific disease and a SNP to any inflammatory disease. It would be unpredictable because each disease is genetically different and it is unpredictable that a change in one amino acid sequence would be able to detect any of these diseases because it is unclear if the amino acid sequence change is detectable in any disease. The art teaches that extrapolation to any disease is unpredictable. As discussed below Witte et al. that there was no statistically significant correlation between NcoI LT-A mutation and asthma.

The specification only provides disclosure of detection of mutations in a human population, however, the claims broadly encompass any mutation in any LT-α gene in any organism. This would include dogs, cats, peacocks, and hamsters. The specification does not provide guidance as to if there are LT-α gene in other species such as in dogs, cats, peacocks, and hamsters. It is unpredictable that the same correlation between the mutations in humans can be extrapolated to other organisms.

The specification asserts that the expression level is significantly higher where codon 26 encodes threonine versus encoding asparagine (p. 13 1st full paragraph). The specification in figure 5 discloses that TNF-inducing activity and Selectin

E0inducing activity in human coronary-artery endotheilial cells express mRNA coding for threonine significantly higher than mRNA encoding for asparagine. However, Claim 12 is drawn to analyzing any expression state of the gene by detection of SNP at nucleotide 80. A change in this SNP position will not produce a change from threonine to asparagine. Further, the claim is not drawn to detection of changes in expression between the two mRNAs which code for different amino acid sequences.

In summary, the claims are drawn to determining any inflammatory disease. The specification however only discloses the correlation of one inflammatory disease, myocardial infarction. The art, as discussed below, teaches that extrapolation of one correlation between a specific disease and a specific SNP is unpredictable. Further the post filing art teaches that the correlation of myocardial infarction and the codon change T26N (threonine to asparagine) is not predictable associated.

Therefore the skilled artisan would have to perform undue experimentation in order to correlate any polymorphism in the LT-A gene to any inflammatory disease. There would be many intervening steps the skilled artisan would have to perform without any guarantee of success to practice the invention as broadly claimed.

Working Examples

The specification provides a Japanese population in which 1133 patients have been diagnosed with myocardial infarction (p. 23 last paragraph. P. 24 1st paragraph). The specification asserts that SNP were detected using the invader PCR assay method

(p. 24).

The specification asserts that 94 myocardial infarction patients were genotypes and the allelic frequency were compared to a population of healthy subjections (p. 26 1st paragraph). 26 SNPs were types and expanded by sample size (p. 27 1st paragraph). Table 1 indications a sample size of 1133 myocardial infarction patients and 1006 control patients. The specification asserts that the population was genotyped (table 1).

Therefore the specification teaches that of the 26 SNPs detected on 1133 myocardial infarction patients only 3 SNPs in LT-A had a statistically significant association. Therefore the specification discloses the unpredictability of associating any SNP in LT-A to any inflammatory disease because of the 26 SNPs detected in the population only 3 were correlated.

For SNP C723A there are three possible genotypes (CC, CA, and AA) (Table 1). The specification discloses that there is a predictable correlation of homozygous (AA) individuals with myocardial infarction compared to homozygous wild type (CC) and heterozygous (CA). Therefore the pvaule discloses in Table 1 is based on the detection of the "A" allele on both strands of nucleic acid. The claims, however, are drawn to detecting one "A" allele. Therefore it is unpredictable that there is a correlation of the allelic mutation based on the correlation of the homozygous AA in the population.

The predictability or unpredictability of the art and degree of experimentation

The applicant's own post-filing work discloses the unpredictability of correlating any mutation with inflammatory diseases. Ozaki et al. (Nature genetics 2002 Vol 32 p.

650) teaches detecting a large number of SNPs in LT-A to determine associations with myocardial infarction (1st paragraph). Ozaki et al. teaches that SNPs with P values less than 0.01 were detected in a larger replication panel and found that most of the loci eventually showed a lack of association with myocardial infarction (p. 650 2nd paragraph). Ozaki et al. teaches that most of the 26 SNPs showed no significant association with myocardial infarction (p. 651 2nd column 2nd paragraph). Therefore the art shows that most mutations of LT-A are not associated with inflammatory disease.

Post-filing art teaches that SNPs in LT-A are not strongly associated with any inflammatory diseases. Witte et al. (European Journal of Human Genetics 2002 Vol 10 p 82) teaches detection of the LT-A ANP of the first intron NcoI recognition sequence in asthma and nonasthmatic patients (abstract). Witte et al. teaches no statistically significant correlation between this SNP and asthma (p. 84 1st paragraph). Therefore Witte et al. teaches that LT-A mutations are not associative to any inflammatory disease.

The art teaches that associations between SNPs in LT-A and inflammatory disease is unpredictable. Trabetti et al. (Journal Med Genet 1999 VOl. 36 p. 323) teaches an association of atopy in asthma patients and the LT-A NocI SNP (abstract). However, Trabetti et al. teaches this same association in other populations (Busselton population) was not observable (p. 324 last paragraph and p. 325 1st paragraph). Therefore Trabetti et al. teaches that in different populations the association of the LT-A mutation with a specific disease in not correlative.

The art teaches that SNP associations to myocardial infarction are unpredictable. Newton-Cheh et a. (JAMA 2004 Vol. 291 p. 3008) teaches that myocardial infaction is a complex trait to which multiple environmental and genetic factors contribute (p. 3008 2nd paragraph). Newton-Cheh et al. teaches that there is also evidence that there are sex differences between male and females with regard to correlation of genetic variants in myocardial infaction (p. 3008 3rd paragraph). Therefore the art teaches the unpredictability of such associations in different populations.

Newton-Cheh et al. teaches that the studies which are published have conflicting results because of population differences (p. 3008 last 2 paragraphs). Newton-Cheh et al. teaches that results are often confounded by baseline covariates (p. 3009 1st column 2nd full paragraph), correlation of genetic variants with other variants that are casual (p. 3009 2nd column 2nd paragraph), and false positive and negatives given the number of SNPs and population sizes (p. 3009 last two paragraphs).

Post-filing art discloses that there is no predictive correlation between myocardial infaction and the elected SNP (e.g. Thr26Asn). Tobin et al. (European Heart Journal 2004 Vol 25 p. 459) teaches a method of detecting SNP from LT-A and the association with myocardial infaction (abstract). Tobin et al. tested 1052 subjects (abstract). Tobin et al. does not teach a statistically significant p-value for SNP thr26asn (p= 0.446) (Table 2 p. 462 last gene and polymorphism). Tobin et al. teaches that though MI was associated with Thr26Asn in other populations it was not in his study (p. 465 1st column last paragraph). Tobin et al. teaches that the difference in association might be due to the different types of populations (p. 465 2nd column 1st paragraph). Therefore even

the statistically significant association of the SNP with myocardial infarction in the instant specification (Table 1 SNP Thr26Asn to myocardial infarction) is not reproducible in other populations.

In summary, the claims are drawn to determination of any inflammatory disease by detection of any mutation in LT-A ; however, the art teaches that such associations are unpredictable and population specific.

Amount of Direction or Guidance Provided by the Specification

The specification does not provide any specific guidance as to how to correlate determination of any inflammatory disease with detection of any mutations in the LT-A gene.

The specification discloses a method of detecting many SNPs from LT-A and correlating the mutations to one specific inflammatory disease (myocardial infarction). The specification teaches that only 3 of the SNPs tested were statistically correlated to myocardial infarction.

The specification does not teach a polymorphic change at position 80; rather, the amino acid change disclosed in the specification is not encompassed by a mutational change at position 80.

The specification does not teach which mutations are associated with inflammatory diseases in any organism.

The art teaches that associations between mutations of LT-A gene and inflammatory disease are unpredictable and population specific. The art teaches that even the mutation T26N is not correlative to myocardial infarction in post filling art.

The skilled artisan, therefore, would have to perform undue experimentation to

determine the association of any polymorphism in LT-A to any inflammatory disease.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters, which would have to be studied prior to being able to practice the claimed invention as broadly as written.

The skilled artisan would have to analyze every possible mutation of the LT-A gene because neither the specification nor the art provides guidance as to which mutations are associated to inflammatory disease. The skilled artisan would have to analyze the correlation of each of these mutations with each inflammatory disease because neither the specification nor the art provides guidance as to extrapolate a correlation of a specific disease to any inflammatory disease. The skilled artisan would then need to test associations in a variety of populations because the art teaches that associations are population specific. The skilled artisan would then need to test other organisms to determine which mutations are correlative in other species.

This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Case law has established that '(t)o be enabling, the specification of a patent

must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the specification does not provide a predictable correlation of detection of mutations of the LT-A gene to determination of an inflammatory disease. Further, the art teaches that such correlations are unpredictable and population specific.

Accordingly, in view of the unpredictability in the art, and the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the claimed invention.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1-3, 5-9 and 12 are rejected under 35 U.S.C. 102(a) as being anticipated by Ozaki et al. (Nature Genetics December 2002 Vol. 32 p. 650).

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

It is noted that this rejection made be withdrawn based on: a submission of the translated foreign priority papers, a 1.131 declaration stating that that reference is not "by others", or arguments that art does not anticipate the pending claims.

With regard to Claims 1-2, Ozaki et al. teaches a method of determining an inflammatory disease (e.g. myocardial infarction) by detection of a polymorphism (e.g. a SNP) of the LT-A gene (p. 650 1st paragraph).

With regard to Claim 3, Ozaki et al. teaches the detection of a C/A polymorphism at nucleotide 80 in the nucleotide sequence of exon 3 of the LT-A gene (described in the art as LT-A exon3 804C to A) (Table 3).

With regard to Claim 5, Ozaki et al. teaches determining an association of myocardial infraction by detecting a gene polymorphism whereby an amino acid to be encoded is mutated from threonine to asparagine by substitution of at least one of the nucleotides 80 to 82 in LT-A (p. 650 1st paragraph and Table 3).

With regard to Claim 6, Ozaki et al. teaches that the method detects myocardial

infarction (p. 650 1st paragraph).

With regard to Claims 7 and 8, Ozaki et al. teaches a method of using a probe to hybridize to the SNP in exon 3 (table 3 and p. 653 last paragraph).

With regard to Claim 9, Ozaki et al. teaches an invader assay which has an forward and reverse primer (p. 653 last paragraph).

With regard to Claim 12, Ozaki et al. teaches detection of the SNP consisting of a C/A polymorphism at nucleotide 80 of exon 3 (table 3).

13. Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Trabetti et al. (Journal Med Genet 1999 VOl. 36 p. 323).

With regard to Claims 1 and 2, Trabetti et al. teaches determining an inflammatory disease (asthma atopy) by detection of a SNP (LT-A NcoI) (abstract).

Conclusion

14. No Claims are allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katherine Salmon whose telephone number is (571) 272-3316. The examiner can normally be reached on Monday-Friday 8AM-430PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Katherine Salmon
Examiner
Art Unit 1634

/Jehanne Sitton/
Primary Examiner
12/13/2007